Image AF/1642

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First Named Inventor	Rosenblatt
Group Art Unit	1642
Examiner Name	Larry R. Helms
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ENCLOSURES *(check all that apply)*

- ☐ Fee Transmittal Form
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- ☐ Amendment / Reply
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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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Signature	Michael L. Goldman — Registration No. 30,727
Date	April 5, 2004

CERTIFICATE OF MAILING OR TRANSMISSION [37 CFR 1.8(a)]

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PATENT
Docket No.: **176/60197 (6-11405-675/676)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Rosenblatt et al.	Examiner: Larry R. Helms
Serial No.	:	09/016,743	Art Unit: 1642
Cnfrm. No.	:	7389	
Filed	:	January 30, 1998	
For	:	CHIMERIC ANTIBODY FUSION PROTEINS FOR THE RECRUITMENT AND STIMULATION OF AN ANTITUMOR IMMUNE RESPONSE	

REPLY BRIEF UNDER 37 C.F.R. § 1.193(b)

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

Pursuant to 37 CFR § 1.193(b), appellants hereby submit, in triplicate, their Reply Brief to the Examiner's Answer, dated February 5, 2004. Although no fees are believed to be due, the Commissioner for Patents is hereby authorized to charge Deposit Account No. 14-1138 for any fees owed.

All arguments set forth in appellants' Appeal Brief of November 4, 2003, are hereby repeated. This Reply Brief is submitted to respond to points made in the Examiner's Answer.

I. Introduction

For the reasons set forth in appellants' Appeal Brief, the rejection of claims 1, 3-8, 10, and 25 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 5,824,782 to Hölzer ("Hölzer") in view of Huston et al., "Protein Engineering of Single-Chain Fv Analogs and Fusion Proteins," Methods Enzymology, 203:46-88 (1991) ("Huston"), the rejection of claims 1 and 9 under 35 U.S.C. § 103(a) for obviousness over Huston in view of U.S. Patent

No. 5,514,554 to Bacus ("Bacus") and Hölzer, the rejection of claims 1, 3-10, and 25 under U.S.C. § 112 (2nd para.) for indefiniteness, and the rejection of claims 1, 3-10, and 25 under U.S.C. § 112 (1st para.) for lack of descriptive support are improper and should be withdrawn. As shown below, the Examiner's Answer provides no basis for maintaining these rejections.

II. The Examiner's Answer Improperly Maintains the Rejection of Claims 1, 3-8, 10, and 25 Under 35 U.S.C. § 103(a) for Obviousness Over Hölzer in View of Huston

In support of their position that the claims were improperly rejected, appellants have presented extensive evidence and arguments that those skilled in the art would not have adapted Huston's single-chain Fv analog technology to whole antibody immunoconjugates like those of Hölzer. In particular, appellants have relied on the Declaration of Seung-Uon Shin Under 37 C.F.R. § 1,132 ("Shin Declaration") to show why, based on avidity, half life, and chemokine carriage, scientists skilled in the field of antibody-based cancer therapeutics would not have adapted single chain Fv analog technology to whole antibody cancer therapeutics. The Examiner's Answer (page 7, line 18 to page 8, line 1) acknowledges that "there are differences between single chain antibodies and whole antibodies," but never addresses the points made in the Shin Declaration. Instead, the Examiner's Answer argues that one does not have to adapt the teachings of Huston regarding single chain antibodies to the whole antibody immunoconjugates of Hölzer. The basis for this assertion is that, according to the Examiner, Hölzer teaches single chain antibodies, as well as whole antibodies, having a chemokine conjugated at the C-terminus where the antigen binding site retains binding to antigens (Examiner's Answer at pages 8-9). The Examiner, therefore, concludes that the only issue is whether one of ordinary skill in the art would conjugate a chemokine to the N-terminus of heavy or light chain of the antibody instead of at the C-terminus of the antibody (Examiner's Answer at page 8, lines 12-14). Appellants respectfully disagree.

The N-terminus of Hölzer's IL-8 is bound to the monoclonal antibody. According to Hölzer, this arrangement was based on the rationale that "[i]t was demonstrated previously that the N-terminal portion of the IL-8 molecule with the highly conserved E-L-R-motif is required for receptor binding and signal transduction" (column 7, lines 41-44). While Huston teaches that the single-chain Fv can be fused at its amino- or carboxy-terminus

to an effector, one of ordinary skill in the art would not adapt this teaching in Huston to Hölzer, because it would undermine Hölzer's expressed command that the entity attached to the antibody be bound at its N-terminus.

Furthermore, there is no basis for combining the teachings of Hölzer and Huston to make the claimed invention. As extensively pointed out in appellants' Appeal Brief (pages 9-11), there are significant reasons why one of ordinary skill in the art would not have considered information relating to immunoconjugates of single chain Fv analogs as relevant to immunoconjugates made from whole antibodies. In particular, due to the significant differences between single chain Fv analogs and whole antibodies with regard to the avidity, half life, and chemokine carriage, scientists skilled in the field of antibody-based cancer therapeutics would have avoided adapting single chain Fv analog technology to whole antibody cancer therapeutics. With regard to all of this evidence in the Shin Declaration, the Examiner's Answer is silent. Having failed to present any contrary evidence, it is clear that there is absolutely no motivation to combine Hölzer and Huston.

Even if Hölzer disclosed a single chain antibody, the combination of Hölzer and Huston would still completely fail to teach the claimed invention. Hölzer only conjugates chemokines at the C terminus of whole antibodies or antibody fragments, while Huston only conjugates at the N-terminus of a single chain Fv analog. Since neither Hölzer or Huston makes a complete antibody conjugated to a chemokine at the N-terminus, their combination fails to teach the claimed invention.

For all these reasons, the obviousness rejection of claims 1, 3-8, 10, and 25 based on Hölzer and Huston is improper and should be withdrawn.

III. The Examiner's Answer Improperly Maintains the Rejection of Claims 1 and 9 Under 35 U.S.C. § 103(a) for Obviousness Over Huston in View of Bacus and Hölzer

With respect to this rejection, the Examiner has taken the position that the combination of Huston, Hölzer, and Bacus would have rendered the claimed invention obvious, in view of his previous arguments regarding the combination of Hölzer and Huston, described *supra*, and Bacus' teachings of monoclonal antibodies to her2/neu (Examiner's Answer at page 12, lines 3-8).

Since Bacus does not overcome the above-noted deficiencies of Huston and Hölzer, the obviousness rejection of claims 1 and 9 over Huston in view of Bacus and Hölzer is improper and should be withdrawn.

IV. The Examiner's Answer Improperly Maintains the Rejection of Claims 1, 3-10, and 25 Under 35 U.S.C. § 112 (2nd para.) for Indefiniteness

The Examiner's Answer (page 13, lines 12-14) states that the phrase "complete antibody" is indefinite because the phrase is not defined in the specification.

Appellants completely disagree. As already pointed out in appellants' Appeal Brief (page 14), the present application describes chimeric molecules having a complete antibody structure in the specification and drawings. Moreover, the term "antibodies" in the present application is defined to include whole antibodies like IgG, IgM, and IgA, as well as antibody fragments. Thus, it is apparent that the phrase "complete antibody" means complete in the sense of having a complete structure, i.e. an antibody structure having V_H and V_L domains as well as constant regions C_H1, C_H2, and C_H3.

Since the present application is more than sufficiently clear on what a "complete antibody" is, one of ordinary skill in the art would readily understand that a complete antibody, like a whole antibody, contains all regions conventionally found in antibodies as opposed to fragments of antibodies. Therefore, the rejection under 35 U.S.C. § 112 (2nd para.) is improper and should be withdrawn.

V. The Examiner's Answer Improperly Maintains the Rejection of Claims 1, 3-10, and 25 Under 35 U.S.C. § 112 (1st para.) for Lack of Descriptive Support

The Examiner's Answer (page 14-15) states that, although the specification describes chimeric molecules having a complete or fully assembled H_2L_2 form, it is still not clear where support for the phrase "complete antibody" can be found because the phrase encompasses many forms of the antibody molecule.

Appellants disagree. As already pointed out in appellants' Appeal Brief (page 16), the present application fully supports the phrase "complete antibody." Furthermore, it is well known by those skilled in the art that a complete antibody would mean a conventional antibody that not only contains V_H and V_L domains but also constant regions C_H1, C_H2, and C_H3.

In view of the knowledge by those skilled in the art regarding the meaning of the phrase "complete antibody" and the fact that the present application clearly teaches the use of complete antibodies, the rejection under 35 U.S.C. § 112 (1st para.) is improper and should be withdrawn.

VI. Conclusion

For the reasons set forth in the Appeal Brief and this Reply Brief, appellants submit that the rejections of the claims under 35 U.S.C. § 103(a), 35 U.S.C. § 112 (2nd para.), and 35 U.S.C. § 112 (1st para.) are improper and should be withdrawn. Accordingly, the final rejection should be reversed.

Respectfully submitted,

Date: April 5, 2004

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April 5, 2004 Ruth R. Smith
Date Ruth R. Smith